# Perspectives on the development of imatinib and the future of cancer research

Brian J Druker



## Imatinib: a personal history

I am incredibly fortunate. To receive an award from the Lasker Foundation, with its preeminent jury, is indeed an honor. But the greatest reward is seeing patients every week in clinic who have benefitted from my work. The life expectancy of these patients was originally three to five years. They are now leading active and productive lives, and many have been with me for over ten years.

My desire to pursue a career in oncology began when I was a medical student, when I took an elective course on the history of chemotherapy. We learned about the cure of childhood leukemia with combination chemotherapy and about the contributions of pioneers such as Sidney Farber and Lasker laureates Emil Frei and Emil Freireich. Despite these breakthroughs, I imagined there had to be a better way to treat cancer, and I wrote in my final essay that only through a molecular understanding of cancer would we be able to more rationally treat the disease. Even though the prognosis for most cancers was quite poor, it seemed to me that there would be great opportunities in cancer research over the next 20 to 30 years, and I wanted to be a part of this.

When I started my training in oncology at Dana-Farber Cancer Institute, we spent most of our time trying to extend our patients', lives, but our tools were limited. We had 5-flurouracil for colon cancer, doxorubicin (Adriamycin) and one of the first targeted cancer agents, tamoxifen, for breast cancer. For prostate cancer, we were testing long-acting androgen antagonists as an alternative to castration. As for patients battling chronic myeloid leukemia (CML), we dreaded each visit. We checked blood counts, looking for the inevitable signs of progression of the disease to a fatal and untreatable acute leukemia, knowing we would have to deliver harsh news. With this background, I decided to pursue a laboratory career and pledged to continue the work until I was confident that I had something to contribute that was a vast improvement over what was then available.

**Figure 1** Members of the Roberts lab. The males in Tom's lab attempted to dress as physicians in honor of Brian's birthday in 1988. Brian and Tom are both in the top row; Brian is first from left and Tom is second from right.

In early 1985, I met with Thomas Roberts at Dana-Farber on the advice of George Khoury[1]. Despite my limited lab background, Tom was willing to take a chance on his first MD postdoctoral fellow. I entered a lab filled with incredible postdocs and graduate students who became my mentors and friends. This group included Helen Piwnica-Worms, David Kaplan, Michael Corbley, Tony West, Connie Gee, Harvey Mamom, Kenneth Wood and David Pallas (**Fig. 1**). All were extremely patient and helpful in advising a relatively green trainee. We also worked closely with the labs of David Livingston and Charles Stiles and had an ongoing collaboration with Lewis Cantley. It was an exciting time in Tom's lab, as many insights into kinase signaling pathways were being discovered. My initial project was to work

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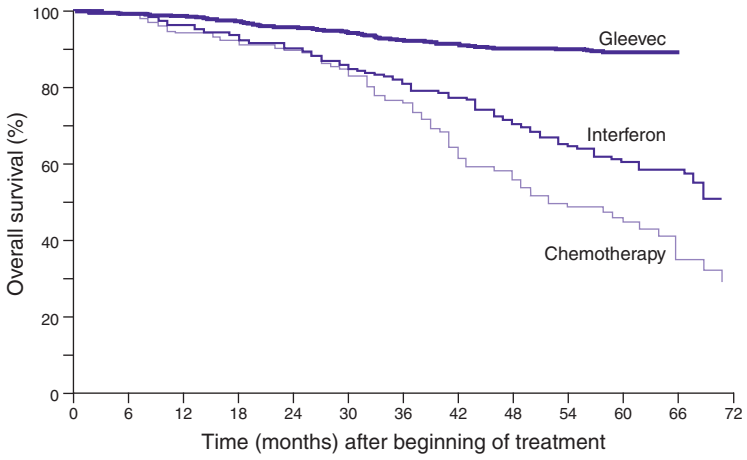


**Figure 2** Survival of patients with CML. Curves show overall survival for patients with CML treated with imatinib (Gleevec)[5], interferon or conventional chemotherapy[24]. Conventional chemotherapy delivers only a minimal effect on survival compared with no treatment.Thanks to C. Lynm for preparing the figure.

on polyoma middle-T antigen and its mechanism of transformation, including its interaction with tyrosine kinases. Soon, Deborah Morrison joined the lab, and, with her expertise and guidance in monoclonal antibody production, I took on a project to develop an antibody to phosphotyrosine. This eventually resulted in the production of 4G10 (ref. 2). My involvement with this antibody led to numerous collaborations with investigators working on tyrosine kinase signaling, and I rapidly gained expertise in this field. When Nick Lydon and Alex Matter at Ciba-Geigy began working with Tom's lab on their kinase inhibitor project, Nick and I formed a natural partnership because of my development of the 4G10 antibody, which was an essential reagent in their screening program for kinase inhibitors.

By 1990, I was at a crossroads in my career. The polyoma project was moving slowly. With my background in oncology and my emerging expertise in tyrosine kinase signaling, it seemed to me that I should be working on a human disease caused by a tyrosine kinase. At the time, the BCR-ABL tyrosine kinase was the best-credentialed tyrosine kinase target in oncology. A couple of years earlier, I had advised Nick that CML, driven by BCR-ABL kinase activity, was likely to be the first and best cancer in which to validate the paradigm of kinase inhibition. With this in mind, I approached James Griffin, with whom I had already been collaborating and, with his guidance, began to develop model systems to study BCR-ABL signaling.

In 1993, I reached another crossroads. I had established various BCR-ABL–driven model systems and had even written a grant with Jim Griffin outlining how to characterize BCR-ABL kinase inhibitors. I was ready to put my knowledge to work in my own lab, and I was fortunate to be recruited by Grover Bagby at Oregon Health & Science University, who shared my vision for targeted therapies. When I moved to Oregon, I had one goal: to find a drug company that had a BCR-ABL kinase inhibitor and to get it into clinic. I was lucky enough that after only one phone call—to Nick Lydon—I had found a willing collaborator with candidate compounds who shared my passion to move a drug into the clinic.

Over the course of the next several years, things moved reasonably smoothly. Of the compounds Nick sent me for testing, I identified CGP 57148B (also known as STI571, Gleevec, Glivec or imatinib mesylate) as the most effective at killing CML cells without harming normal cells[3]. Nick and I worked closely during that time, sharing data, devising experiments and timelines, outlining clinical development plans and discussing challenges. Despite the promising preclinical data, there were still hurdles to overcome before clinical trials commenced. These included concerns about toxicity, whether targeting a single kinase would be an effective anticancer strategy, and whether Ciba-Geigy (now Novartis) would realize a return on their investment for a small-market disease such as CML. In addition, Nick had left Novartis to form his own biotech company. At the time, I was caring for patients in my clinic with CML who had no treatment options remaining. This connection was significant. I became their voice, lobbying my remaining contacts at Novartis, including Alex Matter and Elisabeth Buchdunger, to move this project forward. Ultimately, we prevailed.

As Nick writes in his accompanying commentary (pages 1153–1157), the clinical results with imatinib were nothing short of spectacular. By early 1999, six months after beginning the phase 1 study, we reached effective doses, and virtually all of our patients were responding and experiencing few, if any, side effects[4]. Despite my own concerns about whether responses would be durable, the patients embraced this new therapy. All they knew is that their blood counts were normal for the first time in years. They felt better than they had in a long time and had their hope for the future was restored. Internet chat rooms were a new phenomenon, and patients were describing their experiences with imatinib even before we had presented clinical data or published our results—and the results seemed too good to be true. Now, with five years of follow-up, survival for people with CML treated with imatinib is 89%, compared to less than 50% with previous therapies[5] (**Figs. 2** and **3**). In addition, the risk of relapse has decreased over time, such that no subject randomized to imatinib in a comparative study of imatinib versus interferon plus cytarabine has relapsed in years 6 and 7 after starting therapy[6].

## Translating the success of imatinib to other malignancies

It was an understanding of the target that led to the success of imatinib. What distinguishes imatinib from chemotherapy is that we know which patients will benefit from this drug and why. This was made possible by numerous scientific discoveries that allowed a precise understanding of the molecular pathogenesis of CML[7]. To achieve quantum improvements in cancer outcomes, it is necessary to have a thorough and comprehensive understanding of what distinguishes cancer cells from normal cells, including interactions with surrounding stromal cells. The field is transitioning from an era of empirically based cancer therapy to one based on a precise understanding of the molecular defects in cancer. In the not-too-distant future, clinicians will be able to thoroughly analyze individuals' tumors for molecular defects and match each person with specific, effective therapies that will yield a durable response with minimal toxicity.

To speed this transition, there is a clear need for more funding for cancer research. But researchers also need to reevaluate how funds are spent and to better coordinate their efforts. They need to examine the entire process from target identification to a drug becoming the standard of care and determine, for example, where knowledge deficits exist but technology is available to fill in these gaps. These would be areas where large investments would yield considerable payoffs. There will be other areas where technology has not yet been developed to circumvent the hurdles. In these areas,

substantial and broad investments need to be made that will allow exploration and innovation to find solutions. Researchers already know that there are procedural barriers that slow their progress, and they must work to fix these. Finally, they need to put in place the infrastructure required for a future where personalized cancer therapy is a reality. Workers in the field must have a sense of urgency to their mission, never forgetting the 1.5 million individuals diagnosed and the 500,000 who die of cancer each year and are in desperate need of better therapies.

One area where an immediate large investment would yield a major payoff would be the sequencing of 25,000 pairs of tumor and normal genomes (estimated cost of $1 billion, at $20,000 per genome). This would need to be followed with a similarly massive effort to carry out functional characterization and validation of the targets that might emerge from this effort. With this, the way clinicians understand, classify and treat cancer would change forever. Sequencing cancer genomes and validating targets will not be the panacea for cancer. Some vulnerabilities to cancer will be epigenetically based, others will be based on metabolic susceptibilities, and still others will be based on interactions between tumors and surrounding stroma. Finally, some genomic changes will be in genes that will be difficult to target. Understanding each of these issues will require substantial effort while providing key opportunities for investigator-initiated studies.

The field will continue to confront molecular defects that are difficult to target, including well-validated targets such as *KRAS*, *RB1* and *TP53*. Two basic-research strategies may assist in overcoming this type of hurdle. One is an understanding of signaling mechanisms affected by tumor-causing genes. For example, in lung cancer with mutated *KRAS*, it has been suggested that targeting the phosphatidylinositol-3-kinase and RAF kinase pathways would be equivalent to *KRAS* inhibition[8]. This strategy may be tumor specific, as our lab has seen substantial synergy in acute myeloid leukemia cell lines with these combinations, much more so than in pancreatic cancer cell lines with *KRAS* mutations. A second approach has used a synthetic lethal screen to identify two kinases downstream from RAS that may allow an effective drug development strategy. The synthetic lethal strategy has already shown promise with the finding that inhibition of poly(ADP-ribose) polymerase is an effective treatment strategy for cancers arising in carriers of a *BRCA1* or *BRCA2* mutation or tumors that share features with *BRCA1*-related cancers, such as triple-negative breast cancer[9,10].

**Figure 3** Individuals with CML and their families participating in a Leukemia and Lymphoma Society event. Many of the patients in the photo were treated in the phase 1 and early phase 2 clinical trials of imatinib.

As part of their efforts to accelerate progress, investigators must find ways to encourage academic and industrial collaborations. The development of imatinib is an outstanding example of how academic investigators and industry can form productive collaborations. We each did what we do well. Academics had identified and validated a target, and I had established all the model systems to evaluate compounds. Nick's group had developed compounds and was willing to share their compounds for testing. Then, academics carried out the clinical trials in collaboration with industry. Unfortunately, these types of relationships are hampered by a culture that has evolved in both academia and industry. An example of this is that negotiations go on for months over material transfer agreements, which only slows progress. Academic institutions want to share in the profits, and drug companies want to preserve their ability to recoup an investment. What is desperately needed is a uniform material transfer agreement so that inordinate amounts of time and effort are not wasted on paperwork. It took me six weeks to get imatinib into my lab. At the time, it was already patented against any tumor in a warm-blooded mammal. Had my institution negotiated for royalty rights, it would have delayed progress at best; at worst, this compound would never have made it to my lab or into the clinic.

As medicine move into an era of personalized cancer therapeutics, where cancers are defined by molecular targets instead of site of origin, one concern is that the number of individuals with a specific molecularly defined cancer will be too small for companies to see potential market benefit. Early genomic efforts have suggested that, although large numbers of mutated cancer genes may be identified from these screens, the numbers of pathways implicated in cancer may be finite[11–13]. Regardless, a new paradigm needs to be developed for cancer drug development that allows for rapid approval of drugs that achieve high response rates in a well-defined patient population with an unmet medical need. This would keep drug development costs down but would require additional changes in postapproval safety monitoring, reimbursement policies for off-label use, and a much more nimble clinical-trials system. Much of this was achieved with imatinib in CML and gastrointestinal stromal tumors, but, even for these trials, the approval process could have been faster.

The clinical trials process is cumbersome and needs revamping. Thirty percent of clinical trials at most academic medical centers do not enroll a single subject[14], and many others are not published[15]. The time from protocol conception to enrollment of the first subject can be as long as two-and-a-half years[16]. Funding for cooperative group studies from the National Cancer Institute does not come close to covering costs. What is needed is a much more efficient system that focuses on fewer studies that are well funded, with a quick determination of whether additional investments are worthwhile.

Since the first clinical results of imatinib were presented ten years ago, hundreds of targeted drugs have entered clinical trials,

with numerous examples showing potential, even in patients with advanced solid tumors. For example, the response rate to imatinib for individuals with metastatic gastrointestinal stromal tumors is close to 60%, with a durability of over two years[17]. Similar results are seen with imatinib in the small percentage of patients with melanoma who harbor *KIT* mutations[18]. Rapid and profound responses to epidermal growth factor receptor inhibitors have also been observed in patients with lung cancers driven by *EGFR* mutations[19,20]. At the annual meeting of the American Society of Clinical Oncology in 2009, there was a presentation on an ALK tyrosine kinase inhibitor targeting an ALK fusion protein present in people with lung cancer that elicited rapid and dramatic responses[21]. Similarly, a potent inhibitor of mutant B-RAF showed considerable activity in individuals with melanoma and *BRAF* mutations[22].

In these examples of advanced-phase malignancies, relapses and resistance, as described in Charles Sawyers's accompanying commentary (pages 1158–1161), has been common. For now, combinations of targeted agents with chemotherapy will be used. As our understanding of the molecular pathogenesis of cancer improves, it will be possible to rationally combine targeted therapies. For example, addition of both trastuzumab to the aromatase inhibitor anastrozole and the tyrosine kinase inhibitor lapatinib to letrozole, have markedly improved progression-free survival in individuals with advanced breast cancer positive for estrogen receptor and HER2 (ref. 23). The challenges will be to determine what combinations of targeted therapies will work best, what resistance mechanisms will need to be circumvented, how to serially analyze solid tumors for molecular defects using noninvasive technologies and how to serially analyze for modulation of targets *in vivo*. As learned from the imatinib example, earlier treatment in the course of the disease, when there is less tumor heterogeneity and less chance for resistant mutations to be present, will produce better results. So, with improved early diagnostic technologies, improved outcomes will also be possible, even with single-agent therapy.

Imatinib has created considerable excitement about targeted therapies in both academia and industry. There is still much work to be done in defining molecular pathogenetic events in cancer that will allow for rational combinations of targeted therapies, resulting in improved outcomes for patients. Targeted therapies are important but will not become the exclusive approach to cancer. As clinicians have learned from combating infectious diseases over the past century, they cannot adopt a one-size-fits-all approach. In the 1940s, there was enormous excitement over antibiotics as a cure-all for infections. But there were several events that led to the treatability or eradication of infections. Antibiotics were an obvious breakthrough; vaccinations, another. Public-health measures such as chlorination of water and pasteurization of milk were major contributions. Recast for cancer, these three measures are targeted therapy, immune modulation and preventative measures. Targeted therapies will have a key role, but these will need to be broadly directed to genetic or epigenetic changes in tumors, tumor metabolism, stem cells and tumor-stroma interactions. To effectively manage cancer, clinicians also need innovations in immune therapy and early diagnostics. Ultimately, some of the genetic and epigenetic changes that lead to cancer will have been programmed at birth, and an understanding of these changes will eventually allow molecularly targeted preventative therapies.

I am truly fortunate to have witnessed the advances in cancer therapy over the past decade. Patients and physicians are far more optimistic about our ability to treat cancer. Clinicians and scientists now have the tools at hand to turn cancer into a manageable chronic disease. I am encouraged by what will be accomplished in the coming decades.

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